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Original Research Paper

Human Campylobacteriosis in North-Central Algeria: Epidemiological Features and Multidrug Resistance

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ABSTRACT:
Background: *Campylobacter* spp. is considered the major cause of human bacterial gastroenteritis in the world, with food being the main source of infection. The increase of antibiotic resistance in this species is a threat to public health. **Aim of study**: Is to evaluate the epidemiological features of human campylobacteriosis and the rate of antibiotic resistance. **Material and Methods**: This is a descriptive study conducted in Enterobacteria laboratory in Pasteur Institute of Algeria, Algiers, Algeria from September 2014 to October 2023. This study involved fifty-five patients with campylobacteriosis. Epidemiological information (age, gender, date of onset, infection or carriage, inpatient or outpatient) and laboratory findings (culture, PCR and susceptibility testing) were noted from all patients. **Results**: The most frequently *Campylobacter* species identified was *Campylobacter jejuni* (89.1%) and 40% of the campylobacteriosis cases were reported in the spring trimester. Most cases were observed in children under age five years old (63.6%, $P < 0.05$) and were male (64.5%, $P < 0.05$). High rates of tetracycline (81.8%) and ciprofloxacin (74.5%) resistance in *Campylobacter* spp. have been observed. An increasing percentage (24.5%) of *Campylobacter jejuni* strains simultaneously resistant to ciprofloxacin, tetracycline and erythromycin has been found. **Conclusion**: This study provides for the first time an overview of the epidemiological features and antibiotic resistance of *Campylobacter* strains from North-Centeral Algeria. It also shows an increasing antibiotic resistance, that is serious threat, and worrying multidrug resistance (MDR) rate.

Keywords: Campylobacter jejuni, MDR, Algeria

INTRODUCTION:

Campylobacter species are foodborne zoonotic pathogens, regarded the major cause of bacterial gastroenteritis in humans in both developed and developing countries (1-3).

Campylobacter species are Gram-negative spiral, rod-shaped bacteria with a single or pair of flagella. Most *Campylobacter* species grow under microaerobic conditions. *Campylobacter* species, implicated in human infections, are grouped into major human enteric pathogens: *Campylobacter jejuni* (*C. jejuni*), *Campylobacter coli* (*C. coli*) and *Campylobacter fetus*, and minor pathogens: *C. concisus, C. upsaliensis, C. lari* and *C. hyointestinalis*. In humans, *C. jejuni* and *C. coli* are the main causative agents of campylobacteriosis (1-5). They are commensal organisms frequently isolated from a variety of wild and domestic birds and mammals such as poultry, cattle, sheep, pigs, wild birds, and companion animals (cats and dogs), as well as environment. Poultry is described as the main reservoir of *Campylobacter* spp. (which inhabit the poultry intestines at a level $>10^6$–10^8 CFU/g of poultry faeces) and a common source of transmission of campylobacteriosis to humans (1-5).

The main transmission route to humans is through cross-contamination by the handling, preparation and consumption of contaminated food (2). Other risk factors include the consumption of contaminated undercooked meat, unpasteurized milk and contaminated water, contact with animals and

international travels (5). Other people at high risk of campylobacteriosis include farms and abattoirs workers, due to the lack of hand-washing and food safety practices (3).

Campylobacteriosis is usually characterized as a mild and spontaneously resolving disease. The main symptoms are watery or bloody diarrhea, nausea, abdominal cramps, fever, vomiting and dehydration. Nevertheless, it can occasionally put life at risk and cause severe systematic infections (bacteremia, meningitis, neurological disorders such as Guillain–Barré syndrome and other extraintestinal infections) at extreme ages of life in immunocompromised, diabetic or cancer patients (3, 7).

According to the World Organization of Health, foodborne diseases (including campylobacteriosis) have a considerable burden: every year almost 1 in 10 people is sick. Also, 550 million people are affected each year with diarrheal diseases (including 220 million children under the age of 5 years) (1).

The global incidence rate of *Campylobacter* disease or outbreaks is not known precisely, due to the underreporting of *Campylobacter* infection cases, differences in the notification systems and difficulties with diagnosis (2, 3).

In humans, campylobacteriosis is estimated at 5-14% of all diarrheal disease in the world. Cases of *Campylobacter* spp. infection have increased in North America, Europe, and Australia (2, 3, 8). In the United States of America, the incidence of *Campylobacter* spp. infection in 2015 was 12.97 per 100,000 population (9). In Europe, the notification rate of laboratory-confirmed cases of campylobacteriosis was 66.3 per 100,000 population in 2016 (10). Australia notified *Campylobacter* spp. as the most cause of foodborne infection with 112.3 cases per 100,000 individuals (11). Besides, the lack of data in Africa, Asia and Middle East, some studies indicate that *Campylobacter* spp. infections are also endemic in these areas of the world (2, 3, 7).

The disease is most prevalent in children under the age of five years old, especially males (1-3). A seasonal distribution was described, particularly in summer (1-5).

C. jejuni is the most frequently isolated *Campylobacter* spp. in food and associated to human campylobacteriosis, both in high and low income countries (1-5, 12, 13).

Use of antibiotics is not usually indicated for the treatment of mild campylobacteriosis cases, however severe systemic or chronic infection necessitates antibiotic therapy (14). Therefore, the increase in antibiotic resistance of *Campylobacter* isolates is of concern, particularly resistance to macrolides, fluoroquinolones and gentamicin, which are the drugs of choice for severe campylobacteriosis (14).

Campylobacter spp. has intrinsic resistance to novobiocin, bacitracin, vancomycin, and polymyxins (6).

Azithromycin or erythromycin are the first line of choice for antibiotic treatment of campylobacteriosis. Ciprofloxacin and tetracycline are alternatives but not used for treatment of children (6).

The rate of antibiotic-resistant *Campylobacter* strains, with multi-drug strains, has rise both in developing and developed countries. In this context, the WHO list of priority pathogens for the research and development of new antibiotics includes *Campylobacter* spp. resistant to ciprofloxacin as priority 2 (high) (1-5).

In the last decade, ciprofloxacin, tetracycline and ampicillin resistance rapidly increased in *Campylobacter* spp. in humans in Europe, while erythromycin resistance levels remained relatively low (15).

The increase of multiple and multidrug-resistant *Campylobacter* worldwide is not only attributed to the overuse of antibiotics in human medicine but also in animal farming as growth promotors and to treat and prevent infections (2-5, 12, 16). Especially, antimicrobial resistant *Campylobacter* poses a great risk to human health resulting in therapeutic failures, prolongation of hospital stay, and increase in morbidity and mortality. Previous studies, conducted in Europe and America, showed high rates of antibiotic-resistant *Campylobacter* in animal husbandary and this is a problem of public health concern. In different parts of Africa, various studies conducted in commercial farms have also identified high frequencies of antibiotic-resistant *Campylobacter* in poultry and other livestock (2-5, 12, 16).

In Algeria, studies regarding human *Campylobacter* are very scarce. The first study was published in 1990 addressing Clinical and epidemiological features of human isolates (17); the following studies, published between 2013 and 2020, were mainly focused on prevalence and antimicrobial susceptibility of *Campylobacter* isolated from poultry, sheep and calves (18-21).

The aim of the present study was to address the epidemiological features, the distribution of *Campylobacter* species and the antibiotic resistance, including multi-drug resistance in human *Campylobacter* isolates from North-Central Algeria.

MATERIAL AND METHODS:

Bacterial Isolates:

Fifty-five human *Campylobacter* isolates collected in three cities of North-Central Algeria (Algiers, Blida and Medea), between September, 2014 and October, 2023, were analysed. Isolates were from faecal samples of patients presenting with acute gastroenteritis or asymptomatic carrier patients.

Isolation and Identification of *Campylobacter* spp.:

The strains were grown on Columbia agar plates supplemented with 5% sheep blood and Butzler (Oxoid Limited, Hampshire, United Kingdom) and on

Chromagar Campylobacter agar plates (Chromagar, Paris, France) at 42 °C, under microaerobic conditions (10% CO2, 5% O2 and 85% N2) for 48 h.
Campylobacter spp. were confirmed after subculture, using appearance of colonies, Gram staining, together with biochemical tests such as motility, hippurate hydrolysis, catalase and oxidase tests and API-CAMPY (bioMérieux, Paris, France).

Antimicrobial Susceptibility Testing:
Antibiotic susceptibilities to ampicillin (10 µg), amoxicillin+clavulanic acid (20/10 µg), ciprofloxacin (5 µg), erythromycin (15 µg), tetracycline (30 µg) and gentamicin (10 µg) were determined by the disc diffusion method on Mueller–Hinton agar with 5% sheep blood (Oxoid Limited, Hampshire, UK) and microaerobic environment, based on the Clinical and Laboratory Standards Institute (CLSI) recommendations (22).
C. jejuni strain ATCC 29428 was used as a quality control strain.
Breakpoints were determined following the Clinical and Laboratory Standards Institute (CLSI) recommendations for erythromycin, ciprofloxacin and tetracycline (22), and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) – Comité de l'Antibiogramme de la Société Française de Microbiologie (CASFM) for ampicillin, amoxicillin + clavulanic acid and gentamicin (23).
Multidrug resistance was defined as resistance to three or more non-related antibiotics.

Determination of Minimum Inhibitory Concentrations:
Minimum inhibitory concentrations (MICs) for six antimicrobial agents [ampicillin, amoxicillin+clavulanic acid, ciprofloxacin, tetracycline, erythromycin and gentamicin (bioMérieux, Paris, France)] were determined by the E-test method according to Clinical and Laboratory Standards Institute (CLSI) recommendations (22).
C. jejuni strain ATCC 29428 was used as a quality control strain.
Breakpoints were determined following the Clinical and Laboratory Standards Institute (CLSI) recommendations for erythromycin, ciprofloxacin and tetracycline (22), and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) – Comité de l'Antibiogramme de la Société Française de Microbiologie (CASFM) for ampicillin, amoxicillin + clavulanic acid and gentamicin (23).

Identification of *Campylobacter* Species using Conventional PCR:
DNA was extracted from agar plates using PureLink® Genomic DNA Kit (Invitrogen, Massachusetts, United States) following the manufacturer's instructions. DNA extracts were stored at −20°C until used.
Campylobacter jejuni (F: 5'-GAATGAAATTTTAGAATGGGG-3'; R: 5'-GATATGTATGATTTTATCCTGC-3') and *Campylobacter coli* (F: 5'-ATATTTCCAAGCGCTACTCCCC-3'; R: 5'-CAGGCAGTGTGATAGTCATGGG-3')-specific primers were used as described elsewhere (24, 25).
PCR used a final volume of 25 µL containing 3 µL of extracted DNA, 12.5 µL of Platinum® Multiplex PCR Master Mix, 2x (Applied BioSystems, Massachusetts, United States) and 1 µL of each primer (10 µM) and 3.5 µl of distilled water. Amplification conditions were 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 1 min, annealing at 48°C for 1 min, and extension at 72°C for 1 min and final extension at 72°C for 10 min. Amplicons were separated on 1.5% agarose gels and stained with ethidium bromide. DNA bands were visualized under ultraviolet light.

Statistical Analysis:
Statistical analysis was performedusing IBM SPSS Statistics software version 23 to compare differences in the ratios of infection between patient gender, patient age groups and seasons. $P < 0.05$ were considered as significantly different.

RESULTS:
From September 2014 to October 2023, 55 *Campylobacter* spp. clinical isolates were collected. Most of strains were from outpatients (n=41; 74.5%) than inpatients (n=14; 25.4%) and patients presenting with acute gastroenteritis (n=44; 80%) or asymptomatic carriers (n=11; 20%).
In most of these records, *Campylobacter* spp. was isolated from feces (n=54; 98.2%). In one case from blood (1.8%).
C. jejuni was the most frequent species (n=49; 89.1%), followed by *C. coli* (n=6; 10.9%).
All *C. jejuni* and *C. coli* isolates were confirmed using PCR assay.
The association between campylobacteriosis and gender was statistically significant ($P < 0.05$), with 36 male (65.4%) and 19 female (34.5%). The sex ratio was: 1.9.
The highest number of *Campylobacter* spp. isolates was obtained from children under five years old with 35 cases (63.6%) and was statistically significant ($P < 0.05$) (Figure 1).

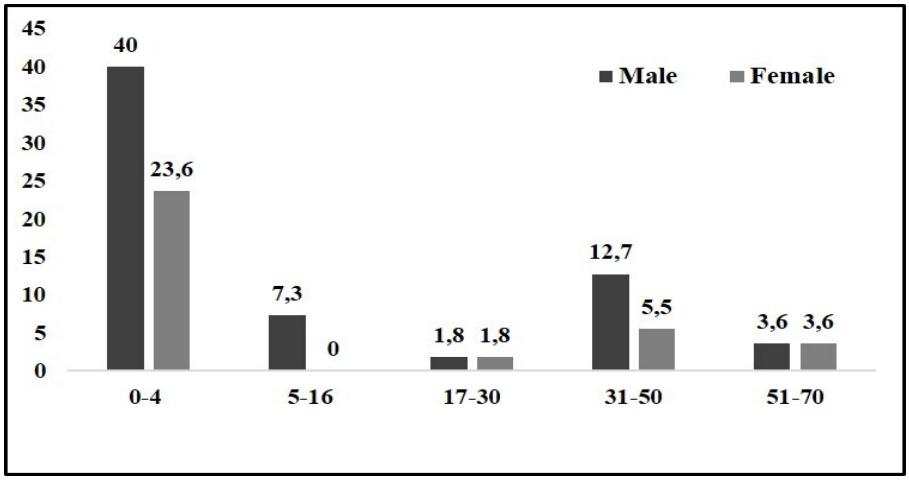

Figure 1: Percentage of distribution of cases by age (years) and gender

Campylobacter spp. isolation showed a spring peak, with an average of 40% of all the cases reported in the March-May trimester, followed by September-November trimester (23.6%) and December-February trimester (20%), with no statistically significant differences (Figure 2).

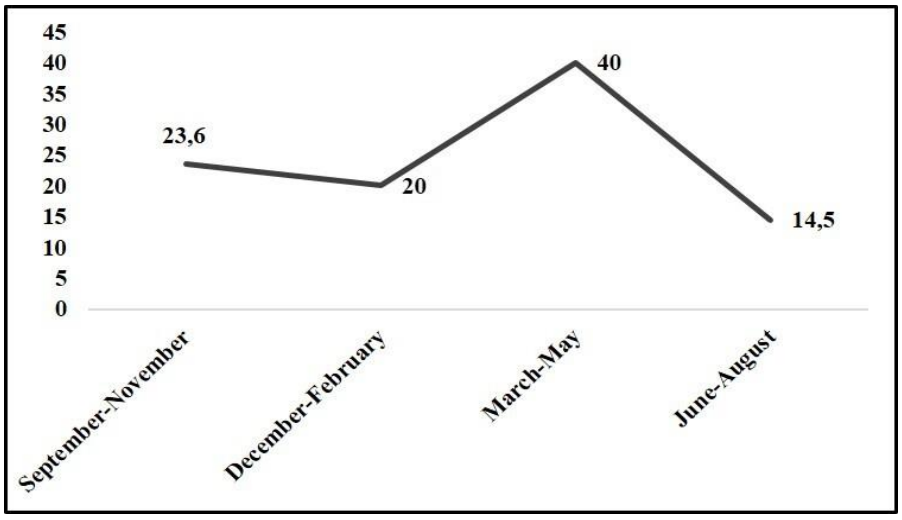

Figure 2: Percentage of Seasonal Distribution of Cases

Campylobacter Antimicrobial Resistance:

Results showed that all the strains were susceptible to amoxicillin+clavulanic acid and gentamicin. Only two (3.6%) strains were susceptible to all antibiotics tested.

Differently, 81.8% of the *Campylobacter* spp. were tetracycline resistant. Many strains were ciprofloxacin resistant (74.5%), ampicillin resistant (41.8%) and less erythromycin resistant (12.7%) (Table 1).

Among 55 *Campylobacter* spp. isolates, 24 (43.6%) were resistant to two, 14 (25.4%) to three and three (5.4%) to four antimicrobial agents, respectively.

The most common resistance patterns were ciprofloxacin-tetracycline for *C. jejuni* (n=18; 36.7%) and *C. coli* (n=5/6) and ciprofloxacin-tetracycline-erythromycin for *C. jejuni* (n=12; 24.5%).

Table 1: Resistance profile to six antibiotics of human *Campylobacter* spp. strains.

Antibiotic	MIC range (µg/mL)	MIC 50%	Resistance rate Number (%)
Ampicillin	0.016-256	12	23 (41.8)
Amoxicillin + clavulanic acid	0.016-8	0.75	0 (0)
Erythromycin	0.125-256	0.75	7 (12.7)
Ciprofloxacin	0.032-256	32	41(74.5)
Tetracycline	0.125-256	256	45 (81.8)
Gentamicin	0.032-0.75	0.38	0 (0)

DISCUSSION:

To our best knowledge, this is the most recent study that analyzed data about the epidemiological features and the antibiotic resistance of human *Campylobacter* species in Algeria. We found that strains were originated from patients presenting with acute gastroenteritis (80%) or asymptomatic carriers (20%). The presence of *Campylobacter* spp. in asymptomatic individuals was described in other studies. It may result from continued exposure to the bacteria, possibly due to poor hygienic-sanitary conditions, and likely, an immunity against the pathogen is developed (2-5). In certain cases, the asymptomatic carriage could be consequence of a resolved infection in which the bacteria continues to be eliminated in the feces. It is well known that *Campylobacter* spp. may be excreted for up to 12 weeks and even to 40 weeks after infection (2). In our study, *Campylobacter* spp. infection occurred in all age groups, but 1–4 years old children were the most susceptible. These results are in accordance with previous data published in developing countries, which showed that *Campylobacter* spp. infections are more frequent in children under 2 years of age, occasionally resulting in death of severe infections. However, in developed countries, there is a bimodal age distribution for campylobacteriosis, the largest peak at 5 years of age and the second peak at 20–29 years of age (2-5). Furthermore, our epidemiological records reported higher distribution in males than in females. Other studies also showed a similar gender difference (26). Seasonality was also observed for campylobacteriosis in Algeria, the incidence strongly increased in the spring period. However, other studies showed that summer trimester was prevalent (26). *C. jejuni* was the most frequent species (89.1%), followed by *C. coli* (10.9%). Similarly, several studies reported the prevalence of *C. jejuni* (2-5, 26, 27). Most *Campylobacter* infections are self-limiting and require only symptomatic therapy. However, the use of antibiotics is essential in some situations such as immunocompromised patients, patients with severe or persistent symptoms, and those with extraintestinal infections (1-5). Macrolides are the drugs of choice. Fluoroquinolones are also recommended as the first-line therapy, whereas tetracyclines are considered a second-line treatment (2-5). Use of antibiotics, particularly fluoroquinolones, in veterinary production is associated with the rise and spread of resistant *Campylobacter* strains, with potential effects on food safety and human health (2-5). Despite the fact that several countries have policy in the control of antibiotics use in animal production, multiples other countries do not have such policy control (2-5, 26).

In our study, a high prevalence of resistance to several antibiotics was observed: tetracycline (81.8%), ciprofloxacin (74.5%) and ampicillin (41.8%). Similarly, very high to extremely high resistance levels to ciprofloxacin were reported in human campylobacter isolates in Europe in 2016 (15). Similarly, in a study conducted in Italy, most of the strains (> 60%) were ciprofloxacin resistant or tetracycline resistant (26).

This quinolone resistance in *C. jejuni* from humans in Europe was associated to resistance in *C. jejuni* from food-producing animals, and to the consumption of quinolones in such animals. For this reason, fluoroquinolones are currently considered as an inappropriate empirical treatment of human *Campylobacter* spp. infections (26).

The resistance to erythromycin in our study was 12.7%. According to the literature, erythromycin resistance is more common among *C. coli* than *C. jejuni*. In Europe, resistance to erythromycin in *C. jejuni* is generally low (1.5%), while it is higher in *C. coli* (14.4%) that can rise to 24.2–54.5% in several countries (27).

Moreover, studies performed in Europe showed that the consumption of macrolides in food-producing animals was associated to resistance in *C. coli* from both food-producing animals and humans. Evenly, resistance in *C. jejuni* from humans was linked to the consumption of macrolides in food producing animals (27).

Similarly, in a study conducted in Italy, a significant rate of macrolides resistant *Campylobacter* strains has been reported (13%) (26). Remarkably, in a study conducted in Portugal, the overall prevalence of resistance to erythromycin whatever the source, human or animal, was 25%. In fact, it has been suggested that this resistance was related to the widespread use of antibiotics in food-producing animals in Portugal, one of the countries with the highest consumption of fluoroquinolones and macrolides among the EU member states (27).

The reason for the increasing importance of macrolides for the treatment of *Campylobacter* infections is that the rates of ciprofloxacin resistance are relatively high for *Campylobacter* species due to the use of antibiotics in the poultry industry and animal husbandry operations. Our results showed that all the strains were susceptible to amoxicillin + clavulanic acid and gentamicin. Gentamicin and amoxicillin + clavulanic acid resistance in *Campylobacter* spp. are rare all over the world (26-30). In EU countries, gentamicin resistance was extremely low with 0.9% resistant strains (27). The detection of gentamicin-resistant strains in food animals and in humans likely reflects the use of aminoglycosides for veterinary treatment (27). In our study, a high percentage of Algerian *Campylobacter* spp. strains was ciprofloxacin-tetracycline resistant (41.8%), 24.5% of *C. jejuni* isolates were ciprofloxacin-tetracycline-erythromycin resistant and 5.4% were ampicillin-ciprofloxacin-tetracycline-erythromycin resistant, which is a public health concern. Multidrug resistant *Campylobacter*

spp. strains are emerging and several studies reported the increase of these strains (3-5, 26-30). In Italy, a high percentage of *Campylobacter* spp. was reported, with 48% of *C. jejuni* and 41% of *C. coli* isolates resistant to two antibiotics (ciprofloxacin and tetracycline) and 29% of *C. coli* isolates were resistant to three antibiotics (ciprofloxacin, tetracycline and erythromycin) (26).
In South Africa, 35.3% of *Campylobacter* strains were resistant to more than two drugs (25).

CONCLUSION:

In conclusion, the present study showed that camplobacteriosis is frequent in male children under the age of five years and *C. jejuni* is the most commonly species isolated from humans in Algeria.
Multidrug resistance in *Campylobacter* spp. is a worrisome problem, with high rates of resistance to antibiotics, particularly ciprofloxacin and tetracycline, and the increasing rate of erythromycin resistance, emphasizing the need for continued monitoring of the antibiotic resistance trends in *Campylobacter* spp.
Regulatory policy should be place on the use of antibiotics both in humans and in food-producing animals, for food safety and public health.
A "One Health" approach, including human, food, animal and environment, is required to improve the management and control of *Campylobacter* spp. in Algeria.

Conflict of Interest: No

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